

# Collagen

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**Collagen** is the main protein of connective tissue in animals and the most abundant protein in mammals,<sup>[1]</sup> making up about 25% of the whole-body protein content.



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## Uses

Collagen is one of the long, fibrous structural proteins whose functions are quite different from those of globular proteins such as enzymes. Tough bundles of collagen called *collagen fibers* are a major component of the extracellular matrix that supports most tissues and gives cells structure from the outside, but collagen is also found inside certain cells. Collagen has great tensile strength, and is the main component of fascia, cartilage, ligaments, tendons, bone and teeth. Along with soft keratin, it is responsible for skin strength and elasticity, and its degradation leads to wrinkles that accompany aging. It strengthens blood vessels and plays a role in tissue development. It is present in the cornea and lens of the eye in crystalline form. It is also used in cosmetic surgery and burns surgery.

Tropocollagen triple helix.

## Industrial uses

If collagen is partially hydrolyzed, the three tropocollagen strands separate into globular, random coils, producing gelatin, which is used in many foods, including flavored gelatin desserts. Besides food, gelatin has been used in pharmaceutical, cosmetic, and photography industries.<sup>[2]</sup> Collagen and gelatin are poor-quality protein since they do not contain all the essential amino acids that the human body requires - they are not complete proteins. Manufacturers of collagen-based dietary supplements claim that their products can improve skin and fingernail quality as well as joint health. However, mainstream scientific research has not shown any evidence to support these claims. Individuals with problems in these areas are more likely to be suffering from some other underlying condition rather than protein deficiency.

From the Greek for glue, *kolla*, the word collagen means "glue producer" and refers to the early process of boiling the skin and sinews of horses and other animals to obtain glue. Collagen adhesive was used by Egyptians about 4,000 years ago, and Native Americans used it in bows about 1,500 years ago. The oldest glue in the world, carbon-dated as more than 8,000 years old, was found to be collagen — used as a protective lining on rope baskets and embroidered fabrics, and to hold utensils together; also in crisscross decorations on human skulls.<sup>[3]</sup> Collagen normally converts to gelatin, but survived due to the dry conditions. Animal glues are thermoplastic, softening again upon reheating, and so they are still used in making musical instruments such as fine violins and guitars, which may have to be reopened for repairs — an application incompatible with tough, synthetic plastic adhesives, which are permanent. Animal sinews and skins, including leather, have been used to make useful articles for millennia.

Gelatin-resorcinol-formaldehyde glue (and with formaldehyde replaced by less-toxic pentanediol and ethanediol) has been used to repair experimental incisions in rabbit lungs.<sup>[4]</sup>

## Medical uses

Collagen has been widely used in cosmetic surgery, as a healing aid for burn patients for reconstruction of bone and a wide variety of dental, orthopedic and surgical purposes. Some points of interest are:

1. when used cosmetically, there is a chance of allergic reactions causing prolonged redness; however, this can be virtually eliminated by simple and inconspicuous patch testing prior to cosmetic use, and
2. most medical collagen is derived from young beef cattle (bovine) from certified BSE (Bovine spongiform encephalopathy) free animals. Most manufacturers use donor animals from either "closed herds", or from countries which have never had a reported case of BSE such as Australia and New Zealand.
3. porcine (pig) tissue is also widely used for producing collagen sheet for a variety of surgical purposes.
4. due to the care in donor animal breeding and selection, as well as the technology used in the preparation of collagen from animal sources, the chance of immune reactions or disease transmission has been virtually eliminated.
5. alternatives using the patient's own fat, hyaluronic acid or polyacrylamide gel are readily available.

Collagens are widely employed in the construction of artificial skin substitutes used in the management of severe burns. These collagens may be derived from bovine, equine or porcine, and even human, sources and are sometimes used in combination with silicones, glycosaminoglycans, fibroblasts, growth factors and other substances.

Collagen is also sold commercially as a joint mobility supplement. This lacks supportive research as the proteins would just be broken down into its base amino acids during digestion, and could go to a variety of places besides the joints depending upon need and DNA orders.

Recently an alternative to animal-derived collagen has become available. Although expensive, this human collagen, derived from donor cadavers, placentas and aborted fetuses,<sup>[5]</sup> may minimize the possibility of immune reactions.

Collagen is now being used as a main ingredient for some cosmetic makeup.

## Composition and structure

The structure of collagen eluded scientists for decades. Many prominent scholars, including Nobel laureates like Watson and Crick and Linus Pauling were known to have been working on collagen structure when it was finally discovered.<sup>[6]</sup> The triple helical structure that is known to be correct in the essentials was proposed by G. N. Ramachandran and Gopinath Kartha in the year 1954.<sup>[7][8]</sup> This proposed structure came to be known as the Madras helix.

The *tropocollagen* or "collagen molecule" subunit is a rod about 300 nm long and 1.5 nm in diameter, made up of three polypeptide strands, each of which is a left-handed helix, not to be confused with the commonly occurring alpha helix, which is right-handed. These three left-handed helices are twisted together into a right-handed coiled coil, a triple helix or "super helix", a cooperative quaternary structure stabilized by numerous hydrogen bonds. Tropocollagen subunits

spontaneously self-assemble, with regularly staggered ends, into even larger arrays in the extracellular spaces of tissues. There is some covalent crosslinking within the triple helices, and a variable amount of covalent crosslinking between tropocollagen helices, to form the different types of collagen found in different mature tissues — similar to the situation found with the  $\alpha$ -keratins in hair. Collagen's insolubility was a barrier to study until it was found that tropocollagen from young animals can be extracted because it is not yet fully crosslinked.

Collagen fibrils are collagen molecules packed into an organized overlapping bundle. Collagen fibers are bundles of fibrils.

A distinctive feature of collagen is the regular arrangement of amino acids in each of the three chains of these collagen subunits. The sequence often follows the pattern Gly-Pro-Y or Gly-X-Hyp, where X and Y may be any of various other amino acid residues. Gly-Pro-Hyp occurs frequently. This kind of regular repetition and high glycine content is found in only a few other fibrous proteins, such as silk fibroin. 75-80% of silk is (approximately) -Gly-Ala-Gly-Ala- with 10% serine — and elastin is rich in glycine, proline, and alanine (Ala), whose side group is a small, inert methyl group. Such high glycine and regular repetitions are never found in globular proteins. Chemically-reactive side groups are not needed in structural proteins as they are in enzymes and transport proteins. The high content of Proline and Hydroxyproline rings, with their geometrically constrained carboxyl and (secondary) amino groups, accounts for the tendency of the individual polypeptide strands to form left-handed helices spontaneously, without any intrachain hydrogen bonding.

Because glycine is the smallest amino acid, it plays a unique role in fibrous structural proteins. In collagen, Gly is required at every third position because the assembly of the triple helix puts this residue at the interior (axis) of the helix, where there is no space for a larger side group than glycine's single hydrogen atom. For the same reason, the rings of the Pro and Hyp must point outward. These two amino acids thermally stabilize the triple helix — Hyp even more so than Pro — and less of them is required in animals such as fish, whose body temperatures are low.

In bone, entire collagen triple helices lie in a parallel, staggered array. 40 nm gaps between the ends of the tropocollagen subunits probably serve as nucleation sites for the deposition of long, hard, fine crystals of the mineral component, which is (approximately) hydroxyapatite,  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  with some phosphate. It is in this way that certain kinds of cartilage turn into bone. Collagen gives bone its elasticity and contributes to fracture resistance.

## Types and associated disorders

Collagen occurs in many places throughout the body. There are 28 types of collagen described in literature. Over 90% of the collagen in the body, however, are Collagens I, II, III, and IV. A simple way to remember their general functions is:

- Collagen One - bONE (main component of bone)
- Collagen Two - carTWOlage (main component of cartilage)
- Collagen Three - reTHREEculate (main component of reticular fibers)
- Collagen Four - FLOOR - forms the basement membrane

Collagen diseases commonly arise from genetic defects that affect the biosynthesis, assembly, posttranslational modification, secretion, or other processes in the normal production of collagen.

Type	Notes	Gene(s)	Disorders
I	This is the most abundant collagen of the human body. It is present in scar tissue, the end product when tissue heals by repair. It is	<i>COL1A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL1A1">http://www.genenames.org/data/hgnc_data.php?match=COL1A1</a> ) , <i>COL1A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL1A2">http://www.genenames.org/data/hgnc_data.php?match=COL1A2</a> )	osteogenesis imperfecta, Ehlers-Danlos Syndrome

	found in tendons, skin, artery walls, the endomysium of myofibrils, fibrocartilage, and the organic part of bones and teeth.		
II	Hyaline cartilage, makes up 50% of all cartilage protein. Vitreous humour of the eye.	<i>COL2A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL2A1">http://www.genenames.org/data/hgnc_data.php?match=COL2A1</a> )	Collagenopathy, types II and XI
III	This is the collagen of granulation tissue, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized. Reticular fiber. Also found in artery walls, skin, intestines and the uterus	<i>COL3A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL3A1">http://www.genenames.org/data/hgnc_data.php?match=COL3A1</a> )	Ehlers-Danlos Syndrome
IV	basal lamina; eye lens. Also serves as part of the filtration system in capillaries and the glomeruli of nephron in the kidney.	<i>COL4A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL4A1">http://www.genenames.org/data/hgnc_data.php?match=COL4A1</a> ), <i>COL4A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL4A2">http://www.genenames.org/data/hgnc_data.php?match=COL4A2</a> ), <i>COL4A3</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL4A3">http://www.genenames.org/data/hgnc_data.php?match=COL4A3</a> ), <i>COL4A4</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL4A4">http://www.genenames.org/data/hgnc_data.php?match=COL4A4</a> ), <i>COL4A5</i> , <i>COL4A6</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL4A6">http://www.genenames.org/data/hgnc_data.php?match=COL4A6</a> )	Alport syndrome
V	most interstitial tissue, assoc. with type I, associated with placenta	<i>COL5A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL5A1">http://www.genenames.org/data/hgnc_data.php?match=COL5A1</a> ), <i>COL5A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL5A2">http://www.genenames.org/data/hgnc_data.php?match=COL5A2</a> ), <i>COL5A3</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL5A3">http://www.genenames.org/data/hgnc_data.php?match=COL5A3</a> )	Ehlers-Danlos syndrome (Classical)
VI	most interstitial tissue, assoc. with type I	<i>COL6A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL6A1">http://www.genenames.org/data/hgnc_data.php?match=COL6A1</a> ), <i>COL6A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL6A2">http://www.genenames.org/data/hgnc_data.php?match=COL6A2</a> ), <i>COL6A3</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL6A3">http://www.genenames.org/data/hgnc_data.php?match=COL6A3</a> )	Ulrich myopathy and Bethlem myopathy
VII	forms anchoring fibrils in dermal epidermal junctions	<i>COL7A1</i>	epidermolysis bullosa

VIII	some endothelial cells	<i>COL8A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL8A1">http://www.genenames.org/data/hgnc_data.php?match=COL8A1</a> ) , <i>COL8A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL8A2">http://www.genenames.org/data/hgnc_data.php?match=COL8A2</a> )	-
IX	FACIT collagen, cartilage, assoc. with type II and XI fibrils	<i>COL9A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL9A1">http://www.genenames.org/data/hgnc_data.php?match=COL9A1</a> ) , <i>COL9A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL9A2">http://www.genenames.org/data/hgnc_data.php?match=COL9A2</a> ) , <i>COL9A3</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL9A3">http://www.genenames.org/data/hgnc_data.php?match=COL9A3</a> )	- EDM2 and EDM3
X	hypertrophic and mineralizing cartilage	<i>COL10A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL10A1">http://www.genenames.org/data/hgnc_data.php?match=COL10A1</a> )	-
XI	cartilage	<i>COL11A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL11A1">http://www.genenames.org/data/hgnc_data.php?match=COL11A1</a> ) , <i>COL11A2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL11A2">http://www.genenames.org/data/hgnc_data.php?match=COL11A2</a> )	Collagenopathy, types II and XI
XII	FACIT collagen, interacts with type I containing fibrils, decorin and glycosaminoglycans	<i>COL12A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL12A1">http://www.genenames.org/data/hgnc_data.php?match=COL12A1</a> )	-
XIII	transmembrane collagen, interacts with integrin α1β1, fibronectin and components of basement membranes like nidogen and perlecan.	<i>COL13A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL13A1">http://www.genenames.org/data/hgnc_data.php?match=COL13A1</a> )	-
XIV	FACIT collagen	<i>COL14A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL14A1">http://www.genenames.org/data/hgnc_data.php?match=COL14A1</a> )	-
XV	-	<i>COL15A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL15A1">http://www.genenames.org/data/hgnc_data.php?match=COL15A1</a> )	-
XVI	-	<i>COL16A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL16A1">http://www.genenames.org/data/hgnc_data.php?match=COL16A1</a> )	-
XVII	transmembrane collagen, also known as BP180, a 180 kDa protein	<i>COL17A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL17A1">http://www.genenames.org/data/hgnc_data.php?match=COL17A1</a> )	Bullous Pemphigoid and certain forms of junctional epidermolysis bullosa
XVIII	source of endostatin	<i>COL18A1</i>	-
XIX	FACIT collagen	<i>COL19A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL19A1">http://www.genenames.org/data/hgnc_data.php?match=COL19A1</a> )	-

XX	-	<i>COL20A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL20A1">http://www.genenames.org/data/hgnc_data.php?match=COL20A1</a> )
XXI	FACIT collagen	<i>COL21A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL21A1">http://www.genenames.org/data/hgnc_data.php?match=COL21A1</a> )
XXII	-	<i>COL22A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL22A1">http://www.genenames.org/data/hgnc_data.php?match=COL22A1</a> )
XXIII	-	<i>COL23A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL23A1">http://www.genenames.org/data/hgnc_data.php?match=COL23A1</a> )
XXIV	-	<i>COL24A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL24A1">http://www.genenames.org/data/hgnc_data.php?match=COL24A1</a> )
XXV	-	<i>COL25A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL25A1">http://www.genenames.org/data/hgnc_data.php?match=COL25A1</a> )
XXVI	-	<i>EMID2</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=EMID2">http://www.genenames.org/data/hgnc_data.php?match=EMID2</a> )
XXVII	-	<i>COL27A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL27A1">http://www.genenames.org/data/hgnc_data.php?match=COL27A1</a> )
XXVIII	-	<i>COL28A1</i> ( <a href="http://www.genenames.org/data/hgnc_data.php?match=COL28A1">http://www.genenames.org/data/hgnc_data.php?match=COL28A1</a> )

In addition to the above mentioned disorders, excessive deposition of collagen occurs in Scleroderma.

## Staining

In histology, collagen is brightly eosinophilic (pink) in standard H&E slides. The dye methyl violet may be used to stain the collagen in tissue samples.

The dye methyl blue can also be used to stain collagen and immunohistochemical stains are available if required.

The best stain for use in differentiating collagen from other fibers is Masson's trichrome stain.

## Synthesis

### Amino acids

Collagen has an unusual amino acid composition and sequence:

- Glycine (Gly) is found at almost every third residue
- Proline (Pro) makes up about 9% of collagen
- Collagen contains two uncommon derivative amino acids not directly inserted during translation. These amino acids are found at specific locations relative to glycine and are modified post-translationally by different enzymes, both of which require vitamin C as a cofactor.
  - Hydroxyproline (Hyp), derived from proline.
  - Hydroxylysine, derived from lysine. Depending on the type of collagen, varying numbers of hydroxylysines have disaccharides attached to them.

### Collagen I formation

Most collagen forms in a similar manner, but the following process is typical for type I:

## 1. Inside the cell

1. Three peptide chains are formed (2 alpha-1 and 1 alpha-2 chain) in ribosomes along the Rough Endoplasmic Reticulum (RER). These peptide chains (known as preprocollagen) have registration peptides on each end; and a signal peptide is also attached to each
2. Peptide chains are sent into the lumen of the RER
3. Signal Peptides are cleaved inside the RER and the chains are now known as procollagen
4. Hydroxylation of lysine and proline amino acids occurs inside the lumen. This process is dependent on Ascorbic Acid (Vitamin C) as a cofactor
5. Glycosylation of specific hydroxylated amino acid occurs
6. Triple helical structure is formed inside the RER
7. Procollagen is shipped to the golgi apparatus, where it is packaged and secreted by exocytosis

## 2. Outside the cell

1. Registration peptides are cleaved and tropocollagen is formed by procollagen peptidase.
2. Multiple tropocollagen molecules form collagen fibrils, and multiple collagen fibrils form into collagen fibers
3. Collagen is attached to cell membranes via several types of protein, including fibronectin and integrin.

## Synthetic pathogenesis

Vitamin C deficiency causes scurvy, a serious and painful disease in which defective collagen prevents the formation of strong connective tissue. Gums deteriorate and bleed, with loss of teeth; skin discolors, and wounds do not heal. Prior to the eighteenth century, this condition was notorious among long duration military, particularly naval, expeditions during which participants were deprived of foods containing Vitamin C. In the human body, a malfunction of the immune system, called an autoimmune disease, results in an immune response in which healthy collagen fibers are systematically destroyed with inflammation of surrounding tissues. The resulting disease processes are called Lupus erythematosus, and rheumatoid arthritis, or collagen tissue disorders.<sup>[9]</sup>

Many bacteria and viruses have virulence factors which destroy collagen or interfere with its production.

## Art

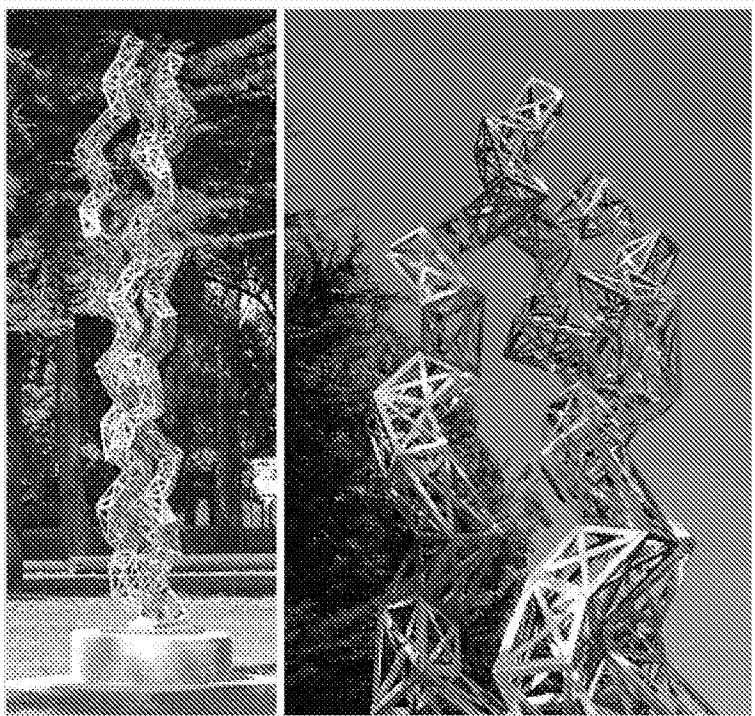
Julian Voss-Andreae has created sculptures based on the collagen structure out of bamboo and stainless steel. His piece "Unraveling Collagen" is, according to the artist, a "metaphor for aging and growth"<sup>[10][11]</sup>.

## See also

- Collagenase, the enzyme involved in collagen breakdown and remodelling.
- Osteoid
- Fibrous protein
- Ehlers-Danlos Syndrome

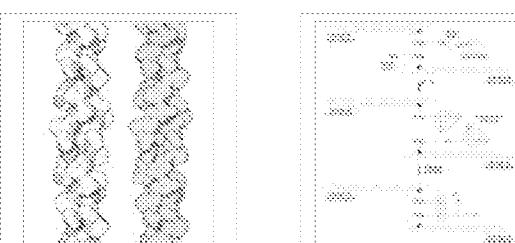
## References

1. ^ Gloria A. Di LulloDagger , Shawn M. Sweeney, Jarmo Körkkö, Leena Ala-Kokko, and James D. San Antonio; Mapping the Ligand-binding Sites and Disease-associated Mutations on the Most Abundant Protein in the Human, Type I Collagen  
(<http://www.jbc.org/cgi/content/abstract/277/6/4223>) ; *J. Biol. Chem.*, Vol. 277, Issue 6, 4223-4231, February 8, 2002
2. ^ Gelatin's Advantages: Health, Nutrition and Safety ([http://www.gmap-gelatin.com/gelatin\\_adv.html](http://www.gmap-gelatin.com/gelatin_adv.html))
3. ^ Oldest Glue Discovered (<http://www.archaeology.org/online/news/glue.html>)
4. ^ *Ann Thorac Surg.* 1994 Jun; 57(6): 1622-7
5. ^ Human or Cadaver-derived Implants (AlloDerm, Cymetra, Dermalogen, Fascian) - All About Lip Augmentation (<http://www.lipaugmentation.com/bioimplants.htm>)
6. ^ GNR — A Tribute - Resonance - October 2001 (<http://www.ias.ac.in/resonance/Oct2001/Oct2001p2-5.html>)
7. ^ <http://www.proteinscience.org/cgi/reprint/10/8/1689.pdf>
8. ^ G.N. Ramachandran - Nature Structural & Molecular Biology ([http://www.nature.com/nsmb/journal/v8/n6/full/nsb0601\\_489.html](http://www.nature.com/nsmb/journal/v8/n6/full/nsb0601_489.html))
9. ^ AJR article about lupus and other collagen disorders (<http://ard.bmjjournals.com/cgi/content/abstract/41/1/33>)
10. ^ Ward, Barbara (April 2006). "'Unraveling Collagen' structure to be installed in Orange Memorial Park Sculpture Garden". *Expert Rev. Proteomics* **3** (2): 174. doi:10.1586/14789450.3.2.169.
11. ^ Interview with J. Voss-Andreae "Seeing Below the Surface" in Seed Magazine ([http://seedmagazine.com/news/2006/05/seeing\\_below\\_the\\_surface.php](http://seedmagazine.com/news/2006/05/seeing_below_the_surface.php))



Julian Voss-Andreae's sculpture *Unraveling Collagen* (2005), stainless steel, height 11'3" (3.40 m).

## Additional images



Collagen

Action of lysyl oxydase  
(in French)

## External links

- The Collagen Protein (<http://macromoleculeinsights.com/collagen.php>)
- Hydrolyzed Collagen (Gelatin) (<http://www.hydrolyzed-collagen.com>)
- 12 types of collagen (<http://web.indstate.edu/thcme/mwking/extracellularmatrix.html>)
- Database of type I and type III collagen mutations (<http://www.le.ac.uk/genetics/collagen/>)
- Science.dirbix Collagen (<http://science.dirbix.com/biology/collagen>)
- Computer-generated animations of the assembly of Type I and Type IV Collagens (<http://www.mc.vanderbilt.edu/cmb/collagen/>)
- The British Association of Cosmetic Doctors - Collagen For Cosmetic Use Information Page (<http://www.cosmeticdoctors.co.uk/fillers.asp>)

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